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NITROGEN MUSTARDS

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I have been asked to speak about a series of new agents that may be encountered in the event of chemical warfare. I call them new, because they were not in the last war, and because they have been developed as a result of research since the last war. By a series of compounds, I mean that there are five, or six, or more compounds closely related chemically, physiologically, and toxicologically. These compounds are known as nitrogen mustards. The formulas for the nitrogen mustards are secret.

Now, because I am speaking of new compounds the lecture necessarily has certain limitations. In the first place, since I am speaking of a series of compounds which show some variability in action, I must generalize in giving the properties of a class rather than any of the individual members of the series; that is necessary in order to save time. And secondly, because the compounds are new and have not been investigated for twenty-five or thirty years, as mustard and phosgene and chlorpicrin have, much of the information which I shall give is sparse and has been obtained with laboratory animals. It is necessary to extrapolate from laboratory animals to man. In most cases, I think this extrapolation is quite justified, particularly because the data I will present have been obtained with five or six species of animals, varying from the ordinary laboratory mouse up to and including the monkey.

Dr. McLean has pointed out that the vesicants of which we are speaking as a class are much more than vesicants; that is, they are pulmonary irritants, they cause eye damage, and they are systemic poisons. All of those characteristics hold for the nitrogen mustards as well as for mustard itself.

The nitrogen mustards are also persistent agents. The persistence will vary with the particular nitrogen mustard. The most volatile member of the series which is known is five times as volatile as mustard, consequently its persistence will be less. Heavy contamination with the vapor of the most volatile nitrogen mustard will last for two or three hours. On the other hand, the less volatile members are half or less than half as volatile as mustard, consequently they will persist much longer. With these members of the series the vapor may be relatively insignificant relative to the droplets of liquid which may land on machinery, on personnel, or the terrain. Some of the members have so little volatility that we may expect their use as aerosols. They will very likely be dispersed as atomized spray rather than in the form of vapor.

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All of the nitrogen mustards have considerable vesicant action, and they are systemic poisons in exactly the same way that mustard is a systemic poison; that is, large amounts may affect the nervous system, the gastro-intestinal tract, and the hemopoietic system.

I may say at the outset that none of the nitrogen mustards is more toxic than mustard itself. If we speak of the toxicity in terms of different organs which may conceivably be affected, we will find that the nitrogen mustards are not as good vesicants as mustard. They definitely are vesicants, but they are not quite as good as mustard; let us say half or a third as potent as mustard.

On the other hand, the effects on the eyes are perhaps somewhat stronger than in the case of mustard. I will speak somewhat more about the eye damage later, and Dr. Hughes tomorrow will speak to you also quite extensively on the subject.

So far as the respiratory tract is concerned it seems from the information gained that we can say that the most toxic member of the nitrogen mustards is not more toxic than mustard itself.

Well, then, why concern ourselves with nitrogen mustards? I do not profess to be a military expert in any sense, but there are certain advantages which I think will be fairly evident. Perhaps the greatest offensive advantage to these compounds is that, insidious as mustard is, the nitrogen mustards are still better in this direction. They have practically no odor. The odor would be very easy to mistake, even to the trained observer. The individual odors of the series may vary from practically odorless to mildly fishy and perhaps something like soft soap. These odors are quite easily overlooked.

Another offensive advantage to the nitrogen mustards is that they are perhaps a little more difficult to decontaminate with the usual decontaminants. Finally, the greatest offensive advantage to the nitrogen mustards, and this is common to almost any new warfare agent, is simply that they are new and that they are consequently novel in chemical warfare.

It is not necessary to obtain an agent which is more toxic than mustard, in the same way that it is not necessary to obtain a new bacterium which is more toxic than tetanus bacteria to cause trouble to clinicians. The nitrogen mustards are toxic enough to cause serious damage to those who are not acquainted with their properties.

The nitrogen mustards, as I have said previously, are more difficult to decontaminate than the usual agents, and they are even more insidious particularly since they are new. In a sense, this is a prophylactic lecture in which I shall attempt to acquaint you with a few characteristics of these compounds, so that we might be able to work more efficiently and more quickly in case of an attack with these agents.

I should perhaps speak first of protection. As Dr. McLean has pointed out, with the vesicants protection is much more important than therapy. Once you have been burned you are burned and there isn't much that can be done about it. On the other hand, so far as protection is concerned, the protection of the gas mask and impermeable clothing is quite as good for the nitrogen mustards as it is for mustard itself.

The difficulty, of course, is to know when to put the gas mask on. Since these agents have little smell, it is necessary to rely upon the chemical indicators which are available. The chemical indicators can detect concentrations below that which will cause damage.

Now, I would like to say something about the results of exposure to these various compounds since usually gas casualties are to be expected in case these or any other agents are employed. I would like to consider the symptoms and treatment in terms of increasing concentrations. Thus we may begin with a very low concentration, a concentration which would be extremely difficult to detect, and which would have slight effect. Certain symptoms are to be expected with such low concentrations but as the concentration goes up, various other phenomena may occur, and I will try to develop the new symptoms in terms of concentration.

I may say at the outset, that of all the organs and tissues of the body the eyes are most sensitive to these agents, the respiratory tract comes next, and the skin, the hemopoietic system, the central nervous system and the G. I. tract are less susceptible. If we begin with non-lethal concentrations, which are at the limit of detection, at least by odor, we may consider concentrations of five to ten micrograms per liter of air. A concentration of five to ten millionths of a gram per liter of air with an exposure period of five to ten minutes, is not lethal. But eye damage can and does occur as a result of a five to ten minute exposure to concentrations as low as this.

The eye damage has an insidious background. Even more than with mustard, there are no immediate signs of irritation when the eye is exposed to a low concentration of the compound. One may be quite comfortable and unaware in a concentration high enough to cause eye damage. One or two hours after exposure there may be a mild irritation and perhaps the beginning of lacrimation as a result of exposure, but examination of the eye will show no objective signs at all for two or three hours.

After several hours there begins intermittent pain, lacrimation, and irritation, which come and go for a period of perhaps six to eight hours. At the end of this time, examination of the eye will show mainly a conjunctival reaction; i.e., an edema of the conjunctiva. At the end of about eight hours the pain becomes quite severe and is

continuous. At the end of ten to twelve hours there will be a miosis, and the pupil will be markedly contracted. If atropine is instilled in the eye to relieve the miosis, then the pain and headache will go also. There will be at this time a beginning mild corneal haziness or clouding, which is only superficial, and slit lamp examination will show that it is exterior to Bowman's membrane.

The prognosis in damage of this type is quite good. In the absence of any secondary infection it would be expected that within eight to ten days the eye will heal completely, there will be no scarring and practically no injury to sight.

With concentrations of this type it would be expected that respiratory damage would be very small. What one should expect would be usually a mild rhinitis and mild bronchitis. These occur and because of the nature of the compound, may be expected to remain for as long as two weeks before clearing up.

Might I return to the atropine just briefly to note that for some reason the headache and pain which are associated with miosis disappear with atropine. That is symptomatic treatment and will not correct the eye damage, but at least it will make the patient more comfortable.

When we consider higher concentrations, concentrations of the order of one-tenth to two-tenths of a milligram per liter of air, dangerous and lethal effects may be expected. The eye damage is much more severe, and will be described in detail tomorrow. I might say that the cornea becomes very cloudy, photophobia and pain are present, and there is not much than can be done in the way of therapy. If secondary infections are avoided by the use of one of the sulfonamide drugs, then recovery can occur in ten to twelve weeks. The cornea may still remain permanently scarred, and there may be some impairment of vision. But, on the other hand, in the absence of infection complete blindness would not be expected as a result.

I have some slides which I am quite sure you will see again tomorrow. I might just point to a few to give you an indication of the damage that occurs.

That is a rabbit eye, and this photograph was taken about three hours after 1.2 milligrams of one of the nitrogen mustards was instilled into it. Except for the reddening of the conjunctiva, there isn't much in the way of damage.

The next slide was taken three weeks later. I think that the clouding of the cornea is quite evident, and you may see the exfoliation of the corneal epithelium.

The next series shows the progressive damage to a rabbit's eye as a result of exposure to the saturated vapor of one of the nitrogen mustards. The first photograph was taken within an hour, and except for mild conjunctival injection there is very little that can be seen. The second photograph was taken three hours after exposure and shows some conjunctival edema. The next was taken four days after, and shows the corneal clouding. This, I believe was stained with fluorescein, and indicates nicely the damage to the cornea.

This next photograph was taken fourteen days after and you can see the beginning of blood vessel formation in the cornea.

The last slide was taken thirty days after exposure to the vapor. That eye is irreparably damaged. The cornea is cloudy and ulcerated and it is expected that it will remain this way throughout the life of the animal.

The concentrations which will cause eye damage as severe as those indicated in the slides will also cause respiratory symptoms much the same as those which will be found as a result of poisoning.

There will be manifest a severe bronchitis, possibly aphonia and in very severe cases a pulmonary edema generally accompanied by bronchial pneumonia. There isn't much that one can do about the treatment. The patient may possibly be made somewhat more comfortable by inhalation of steam to relieve the congestion of the larynx and trachea. If there is a cough, codeine can be administered to relieve the coughing, and in the case of lung edema possibly oxygen will have a certain degree of value. The bronchial pneumonia which is a complicating factor should be treated as bronchial pneumonias generally are. Just as there is a delayed action in the development of eye symptoms, so is there a delayed action in the development of the respiratory symptoms.

With experimental animals in the laboratory we uniformly find that the majority of deaths will occur four to five days after exposure. There may be very few symptoms for the first twenty-four hours, and the symptoms become progressively worse for periods as long as two weeks. If pulmonary edema and bronchial pneumonia are present, the prognosis is not good.

Concentrations causing very severe eye and respiratory damage will generally cause skin symptoms and symptoms in the hemopoietic system. The skin may be very red and edematous. The lesions are somewhat more superficial than those obtained with mustard, but much of the same type, and so far as treatment is concerned there isn't much than can be done except possibly to relieve the pain and itching with a local anesthetic ointment. If blisters are present, the blisters should not be opened except under conditions of very rigid asepsis. If they are opened, they should be covered with sterile dressing and secondary infection should be avoided.

Now, the effects on the hemopoietic system are rather striking. Exposures to a dangerous concentration will cause a very marked leukopenia. Following a heavy exposure there may be a very transitory leukocytosis. It is very transitory, and will generally last for less than twenty-four hours. This is followed by a precipitous drop in the total white blood count, until at the end of four or five days it is possible to get leukocyte counts as low as two or three hundred. Such low values are to be found only with lethal concentrations. On the other hand, it might be expected that counts as low as two or three thousand could be obtained with lower doses. The differential count shows that the lymphocytes drop immediately, while the heterophils show the transitory rise followed by agranulocytosis.

In terms of prognosis, leukocyte counts below two thousand will be quite dangerous, and those below one thousand are usually lethal. On autopsy the bone marrow shows a complete aplasia.

The symptoms that I have given are in terms of exposure to different concentrations of vapor. It is possible, of course, to be exposed by routes different from vapor.

For example, if the skin is exposed, possibly by directing small droplets of liquid on it, we may find no eye damage at all. On the other hand, there will be certainly skin damage and enough may be absorbed to cause even leukopenia.

If some liquid material is instilled into the eyes, there will be very serious edema and eye damage, but no respiratory, skin or hemopoietic damage.

In general, considering the exposure to the vapor, one may say safely that the eye symptoms are the first to occur and occur with the smallest concentrations. These are followed by the respiratory symptoms and then by other symptoms.

The nervous system is affected to different degrees by varying concentrations. The initial effect on the nervous system is cholinergic in type and can be treated by atropine. That is, there will be salivation, a congested intestine, diarrhea and so forth. These symptoms and some others may possibly occur in very low concentrations.

On the other hand, after a certain concentration is reached the animal may show a flaccid paralysis, which can become fully generalized, and in such cases the animal is generally lost.

The nitrogen mustards may possibly be used for water contamination, and they can cause significant gastrointestinal symptoms. They may cause pain, vomiting, bloody diarrhea and so forth. There isn't much than can be done for those symptoms, except again to make the patient comfortable, perhaps with barbiturates or the use of atropine.

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Now, I might turn from that and say something about first aid. To begin with, the nitrogen mustards, as well as with mustard itself, cannot be treated by first aid when there is a vapor contamination. If there is vapor contamination, first aid will be quite useless.

On the other hand, if there are drops of material placed upon the skin, and one can get at them within one or two or possibly a maximum of five minutes, then a certain amount of good may be done. In contrast to mustard itself, the usual ointment issued by the army does not decontaminate the nitrogen mustards. It simply dilutes it. The removal of droplets from the skin can be effected very well by the dabbing technique, and Dr. McLean has mentioned the use of organic solvents. In the absence of organic solvent, one may prescribe soap and water and lots of it.

If the liquid agent enters the eyes, there is a very nasty problem. The only thing which can be done is to irrigate the eye as much as possible and as quickly as possible. I think that in all cases where the material is actually dropped into the eye the prognosis will be quite bad, and blindness may well result, unless the agent is removed in less than two minutes, and removing the agent quantitatively in less than two minutes is almost impossible.

There is very little more which can be said about the nitrogen mustards, and I might therefore attempt to once more give a symptomatic summary. With vapors the eyes are the organs which are most easily affected and by the lowest concentrations. Higher concentrations may cause respiratory involvement, and in most cases death from vapor will occur as a result of respiratory involvement. If the liquid is encountered, vesication and damage to the particular tissue which is exposed will undoubtedly result. If the material is ingested, gastrointestinal and nervous symptoms will result.

For the purpose of diagnosing exposure to the nitrogen mustards the leukopenia may be useful, for although it is much of the same nature as caused by mustard, it is more severe.

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